Nucleophilic Opening of a Polycyclic Aromatic K-Region Epoxide

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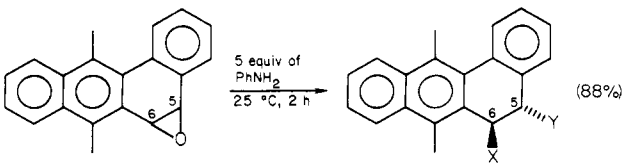
7,12-Dimethylbenz[*a*]anthracene (DMBA) is one of the most potent polycyclic aromatic hydrocarbon (PAH) carcinogens;[1] in fact, DMBA-induced tumors are commonly used in cancer research. Such important biological activity has been attributed to various metabolites of DMBA, including 7-(hydroxymethyl)-12-methylbenz[*a*]anthracene,[2] DMBA bay-region dihydrodiol epoxides,[3] and the K-region DMBA 5,6-oxide.[4] Although current thinking is that DMBA bay-region dihydrodiol epoxides are the most carcinogenic metabolites, a significant role for the K-region epoxide in carcinogenesis cannot be ruled out. For example, the finding that 5-fluoro DMBA is only weakly carcinogenic led to the conclusion that the 5-position of DMBA "is probably involved in carcinogenesis,"[5] and DMBA 5,6-oxide was indeed shown to be capable of transforming mouse fibroblasts in vitro[6] and of initiating tumors in mice.[7] Recently several DMBA 5,6-oxide adducts with guanosine residues of both DNA and RNA have been reported.[8] It seemed appropriate, therefore, to pursue our interest in nucleophilic opening of epoxides[9] by studying the behavior of DMBA 5,6-oxide toward various nitrogen, oxygen, and sulfur nucleophiles under homogeneous and heterogeneous conditions and thus to learn more about the fundamental chemistry of K-region epoxides. We report here the results of this investigation on the synthetically useful, alumina-promoted, nucleophilic opening of DMBA 5,6-oxide as well as the surprising and perhaps biologically significant finding that under nonaqueous homogeneous conditions aniline is enormously more effective than the more basic benzylamine in adding to DMBA 5,6-oxide.

Results and Discussion

A. Homogeneous Reactions. Typically, studies on nucleophilic opening of K-region epoxides by amines have involved prolonged reaction times at ambient temperature and/or shorter periods of reflux in aqueous tetrahydrofuran; nonaromatic amines have been preferred over aromatic amines presumably due to the relatively higher nucleophilicity of the former.[10] Because the basicity and nucleophilicity of the amino group of aniline match those of the biologically important 2-amino group of guanine,[4b,11] we treated DMBA 5,6-oxide with 5 equiv of aniline in anhydrous diethyl ether solvent at 25 °C for 2 h; product isolation and characterization revealed exclusively trans adduct formation in 88% yield, with a 4:1 regioselectivity for nucleophilic attack at position 5 vs. 6 (eq 1). When



1, X = OH; Y = PhNH
2, X = PhNH; Y = OH

(1)

a similar reaction was conducted in deuterated diethyl ether and monitored by ^{1}H NMR, however, no adduct formation was observed even after 24 h. Upon concentration (25 °C; 30 mmHg), removal of excess aniline under high vacuum (45 min; 25 °C), and subsequent reexamination by ^{1}H NMR, conversion of the epoxide to the same regioisomeric adducts as in eq 1 was observed. Thus, aniline adducts are formed during the concentration step. DMBA 5,6-oxide was treated with 5 equiv of aniline *in the absence of any solvent* to confirm this conclusion; after 2 h at 25 °C, ^{1}H NMR analysis indicated essentially quantitative adduct formation in the same regioisomeric ratio as in eq 1.

These results stand in sharp contrast to the corresponding reactions using more nucleophilic benzylamine and *n*-butylamine in place of aniline; under the same conditions as shown in eq 1, followed by concentration under vacuum at 25 °C, no reaction whatsoever was observed! Likewise, 5 equiv of *neat* benzylamine and of *neat* *n*-butylamine at 25 °C for 2 h failed to add to DMBA 5,6-oxide to any appreciable extent. The exceptional ability of aniline to add to DMBA 5,6-oxide[12] suggests that a π-donor–π-acceptor complex might be involved. Indeed, π-stacking has recently been shown to be a critical factor in interaction of a PAH epoxide and a phenol.[13]

Besides the significance of these results as a convenient method for preparing arylamine adducts with K-region PAH epoxides, the unexpectedly high reactivity of aniline toward DMBA 5,6-oxide in a nonaqueous organic medium may serve as a general model for the high and selective reactivity of the exocyclic amino group of guanine toward

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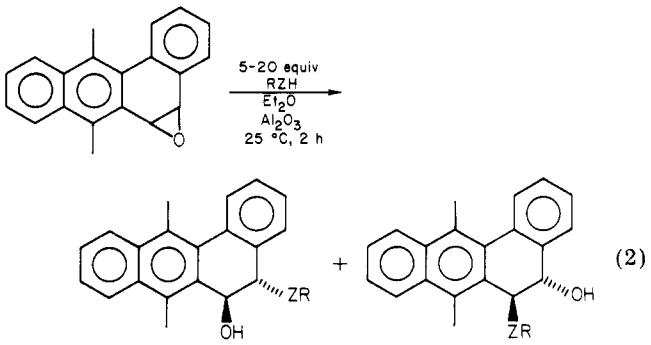
epoxides of PAH's intercalated in DNA.[14]

B. Heterogeneous Reactions. Although a homogeneous *solution* of aniline in diethyl ether does not open DMBA 5,6-oxide effectively at 25 °C within 2 h, in the presence of alumina at 25 °C[9] (or even at −20 °C) for 2 h, aniline adds to DMBA 5,6-oxide to produce trans adducts in 83% yield, with a 2:1 regioselectivity for nucleophilic attack at position 5 vs. 6 (eq 2). This relatively larger



(2)

3 4

RZH	3:4	yield of 3 + 4, %
$PhNH_2$	67:33	66
$PhCH_2NH_2$	60:40	76
n-$BuNH_2$	75:25	88
MeOH	78:22	97
HOH		59
t-BuSH	25:75	30

amount of C-6 attack by aniline under heterogeneous conditions is consistent with alumina's acidic sites coordinating with and activating the epoxide and thereby increasing the electrophilic character of C-6 more than that of C-5.[15] The general ability of alumina to activate epoxides toward nucleophilic attack[9] was demonstrated also by addition of benzylamine, *n*-butylamine, methanol,[16] water, and *tert*-butyl mercaptan to DMBA 5,6-oxide at 25 °C (eq 2). Especially significant aspects of eq 2 are as follows: (1) although benzylamine, *n*-butylamine, methanol, water, and *tert*-butyl mercaptan did *not* add to DMBA 5,6-oxide under the *homogeneous* conditions used in eq 1, high yields of adducts were generally obtained under the *heterogeneous* conditions of eq 2; (2) only 5–20 equiv of RZH species are needed to produce adducts efficiently; (3) for the hard nitrogen and oxygen nucleophiles,[17] regioselective attack occurred at C-5 of DMBA 5,6-oxide, which is sterically more accessible than C-6; (4) with the soft sulfur nucleophile, regioselective attack occurred at the more electrophilic (i.e., softer) C-6 position.[16] Taken together with our previous results,[9] these heterogeneous alumina-promoted additions of structurally simple organic amines, alcohol, water, and mercaptan to a biologically very important PAH K-region epoxide represent a mild, effective, and efficient synthetic method that may be useful also in preparing adducts between PAH epoxides and various biological nucleophiles.[18]

Experimental Section

DMBA 5,6-oxide was prepared as described by Harvey, Goh, and Cortez.[19] Diethyl ether was freshly distilled from the sodium ketyl of benzophenone. Methylene chloride and methanol were used as received from Baker. Aniline and *n*-butylamine were twice distilled before use and the heart-cut was employed. Benzylamine and 2-methyl-2-propanethiol were used as received from Aldrich. Woelm-200-B alumina, acitivity Super I, was the gift of Woelm Pharma. Preparative thin-layer chromatography (TLC) was performed with Analtech silica gel GF plates which were oven-activated for a minimum of 1 h at 120 °C prior to use. Visualization of developed plates was accomplished *via* fluorescence quenching (254 nm). Proton nuclear magnetic resonance (^1H NMR) spectra were obtained at 80 MHz (Varian CFT-20) or 300 MHz (Bruker WM-300). Chemical shifts are reported in parts per million (δ) relative to internal tetramethylsilane (δ = 0.000) in deuteriochloroform unless otherwise stated. Melting points were taken on a Mel-Temp apparatus and are uncorrected. Low-resolution mass spectra were determined with an MS-50 spectrometer through the NSF Regional Instrumentation Facility, Middle Atlantic Mass Spectrometry Laboratory.

General Procedures for Alumina Reactions. A thoroughly oven-dried round-bottomed flask equipped with a magnetic stir bar and a septum inlet is allowed to cool under nitrogen and then tared. After being charged with the indicated amount of alumina under an atmosphere of dry nitrogen in a glovebag, the flask is placed under a positive pressure of nitrogen via a needle inserted through the septum inlet. Enough diethyl ether is added to form a slurry and stirring initiated. To the slurry is added a weighed amount of the appropriate doping agent in the minimum amount of diethyl ether necessary to ensure quantitative transfer. After 10 min, DMBA 5,6-oxide (ratio ca. 1 mmol per 15–25 g of alumina) is added via syringe in the minimum amount of diethyl ether required for dissolution and the syringe rinsed with an additional 1–2 mL of solvent which is also added to the reaction mixture. After 2 h, methanol (or ethanol in the case of methanol-doped alumina) is added and the reaction mixture allowed to stir for at least 2 h. The mixture is then filtered and the solvents removed in vacuo.

DMBA 5,6-Oxide on Aniline-Doped Alumina. DMBA 5,6-oxide (0.0341 g, 0.125 mmol) was allowed to react in diethyl ether with 2.1886 of Woelm-200-basic Super I activity alumina doped with aniline (0.0757 g, 0.813 mmol; 6.5 equiv) for 2 h at ambient temperature. Workup followed by preparative TLC (benzene/diethyl ether; 4:1) afforded 0.0202 g (44%) of 5,6-dihydro-6-hydroxy-7,12-dimethyl-5-(phenylamino)benz[*a*]anthracene (1) (R_f 0.56) and 0.0103 g (22%) of 5,6-dihydro-5-hydroxy-7,12-dimethyl-6-(phenylamino)benz[*a*]anthracene (2) (R_f 0.44). Adduct 1: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.2–1.8 (b, 2 H, OH, NH) 2.716 (s, 3 H; 7-Me), 2.992 (s, 3 H; 12-Me), 5.071 (d, J = 3.015 Hz, 1 H; H_5), 5.240 (d, J = 3.015 Hz, 1 H; H_6), 6.67–8.20 (m, 13 H; Ar H). Irradiation of the higher field 7-Me signal (δ 2.716) gave a nuclear Overhauser enhancement (NOE) of ca. 16% for the doublet at lower field (δ 5.240), confirming the assignment of that resonance as the methine of C-6. ^1H NMR (CD_3OD): δ 2.69 (s, 3 H; 7-Me), 2.99 (s, 3 H; 12-Me), 5.02 (d, J = 2.9 Hz, 1 H; H_5), 5.14 (d, J = 2.9 Hz, 1 H; H_6), 6.50–8.25 (m, 13 H; Ar H). Chemical ionization mass spectroscopy showed a base peak of m/e 366 (molecular ion plus one). Anal. Calcd for $C_{26}H_{23}NO{\cdot}0.5H_2O$: C, 83.39; H, 6.46; N, 3.74. Found: C, 83.17; H, 6.44; N, 3.71. Adduct 2: ^1H NMR ($CDCl_3$) δ 1.2–2.0 (b, 2 H; OH, NH), 2.69 (s, 3 H; 7-Me), 2.93 (s, 3 H; 12-Me), 4.81 (d, J = 3.1 Hz, 1 H; H_5), 5.37 (d, J = 3.1 Hz, 1 H; H_6), 6.50–8.25 (m, 13 H; Ar H): ^1H NMR (CD_3OD) δ 2.64 (s, 3 H; 7-Me), 2.95 (s, 3 H; 12-Me), 4.74 (d, J = 3.1 Hz, 1 H; H_5), 5.39 (d, J = 3.1 Hz, 1 H; H_6), 6.48–8.20 (m, 13 H, Ar H). Chemical ionization mass spectroscopy showed a base peak of m/e 366 (molecular ion plus one). Regiochemistry was assigned in a manner analogous to that used for the adducts

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of guanosine and DMBA 5,6-oxide.[4b,8b]

DMBA 5,6-Oxide with Aniline in Diethyl Ether. To a solution of DMBA 5,6-oxide (0.0120 g, 0.0440 mmol) in diethyl ether (1 mL) containing methylene chloride (0.5 mL) was added a solution of aniline (0.0204 g, 0.219 mmol; 5 equiv) in diethyl ether (1 mL). After 2 h, the mixture was concentrated in vacuo at room temperature. Preparative TLC (diethyl ether) of the residue and isolation of the material with R_f 0.62 gave 0.0140 g (88%) of a mixture of adducts 1 and 2 in a ratio of 80:20 (^{1}H NMR).

DMBA 5,6-Oxide on *n*-Butylamine-Doped Alumina. DMBA 5,6-oxide (0.0071 g, 0.026 mmol) was allowed to react in diethyl ether with 0.1516 g of W-200-B alumina doped with *n*-butylamine (0.0114 g, 0.155 mmol; 6 equiv) for 2 h at ambient temperature. Workup afforded 0.0079 g (88%) of a spectroscopically clean (^{1}H NMR) mixture of regioisomeric adducts in a ratio of 3:1; mass spectrum, *m/e* 345 (parent, molecular ion). The major isomer was assigned, in a manner similar to that previously discussed for the anilino derivatives, as *trans*-5-(*n*-butylamino)-5,6-dihydro-6-hydroxy-7,12-dimethylbenz[*a*]-anthracene: ^{1}H NMR ($CDCl_3$) δ 0.75–1.50 (m, 7 H; $(CH_2)_2CH_3$), 1.50–1.75 (b, 2 H; NH, OH), 2.30–2.80 (m, 2 H; CH_2N), 2.81 (s, 3 H; 7-Me), 2.94 (s, 3 H; 12-Me), 4.48 (d, J = 3.3 Hz, 1 H; H_5), 4.93 (d, J = 3.3 Hz, 2 H; H_6), 7.25–8.25 (m, 8 H; Ar H). The minor isomer was assigned as *trans*-6-(*n*-butylamino)-5,6-dihydro-5-hydroxy-7,12-dimethylbenz[*a*]anthracene: ^{1}H NMR ($CDCl_3$) as described above with the exception of δ 3.94 (d, J = 3.2 Hz, 1 H; H_5) and 5.33 (d, J = 3.2 Hz, 1 H; H_6).

DMBA 5,6-Oxide on Methanol-Doped Alumina. DMBA 5,6-oxide (0.0385 g, 0.141 mmol) was allowed to react in diethyl ether for 2 h at ambient temperature with 1.4323 g of Woelm-200-Basic Super I activity alumina which had been doped with triethylamine (0.0200 g, 1.5%) and methanol (0.0627 g, 1.959 mmol; 14 equiv). The usual workup was effected with absolute ethanol and afforded, after filtration of the alumina and concentration of the ethanol in vacuo, 0.0417 g (97%) of a 78:22 mixture of regioisomeric methanolysis products as determined by ^{1}H NMR spectroscopy.[16] Preparative TLC (benzene/diethyl ether; 1:1) gave 0.0301 g (70%) of the mixture (R_f 0.49) in the same ratio as before chromatography. The major regioisomer **3** displayed signals (^{1}H NMR, $CDCl_3$; 300 MHz) at δ 2.8359 (s, 3 H; 7-Me) 2.9576 (s, 3 H; 12-Me), 3.3504 (s, 3 H; OMe), 5.002 (d, J = 3.38, 1 H; 5-H), 5.063 (dd, J = 3.38 and 1.36 Hz, 1 H; 6-H) and those of the minor isomer **4** were δ 2.8212 (s, 3 H; 7-Me), 2.9429 (s, 3 H; 12-Me), 3.3086 (s, 3 H; OMe), 4.428 (d, J = 2.79, 1 H; 5-H), 5.3629 (d, J = 2.79, 1 H; H-6). The remainder of the spectral information for the two isomers was indistinguishable: δ 1.88 (b s, 1 H; OH), 7.32–7.75, 8.10–8.25 (m, 8 H; Ar H).

The regiochemistry of these adducts was assigned on the basis of multiple NOE measurements as follows. Simultaneous irradiation of the 7-Me signals for both **3** and **4** resulted in enhancement of the downfield methine resonances of **3** (ca. 20%) and **4** (ca. 12%), thus establishing these as the 6-H resonance of **3** at 5.063 ppm and the 6-H resonance of **4** at 5.364 ppm. Further, simultaneous irradiation of the methoxy signals of both **3** and **4** caused enhancement of the benzylic protons at C-5 (5%) and C-6 (8%) of **3** while only the higher field methine proton at C-5 of **4** suffered enhancement (8%). Inspection of molecular models revealed that the methine proton of closer proximity to the methoxyl protons for both **3** and **4** is that which resides on that carbon that is adjacent to the methoxy-bearing carbon. Thus, the major isomer **3** is assigned as the 5-methoxy adduct while **4** is assigned as the 6-methoxy isomer in consideration of the magnitudes of the various NOE measurements. That no NOE is associated with the 6-H of **4** may be attributed to the steric congestion which would rise from interaction of the methoxy group with the 7-methyl upon close approach to the 6-H. For the major isomer **3** this type of interaction is not present and as a result both methines are enhanced but to differing extents.

Also, analysis of the chemical shifts of these adducts as described earlier for the adducts of guanosine and DMBA 5,6-oxide[4b,8b] supports these assignments in that the carbon bearing the methoxyl is shifted downfield by 0.26 ppm in **3** and 0.16 ppm in **4** relative to the dihydrodiol while the methines on adjacent benzylic positions in **3** and **4** are shifted *up*field by 0.14 and 0.31 ppm, respectively.

DMBA 5,6-Oxide with Methanol in Diethyl Ether. To a solution of DMBA 5,6-oxide (0.0050 g, 0.0183 mmol) in diethyl ether (1 mL) was added a solution of methanol (0.0121 g, 0.378 mmol; 21 equiv), and triethylamine (0.0011 g) in diethyl ether (1 mL). After 2 h, the volatiles were removed in vacuo. The residue was examined by ^{1}H NMR spectroscopy and consisted of unchanged arene oxide. A virtually quantitative recovery was obtained.

DMBA 5,6-Oxide on Water-Doped Alumina. DMBA 5,6-oxide (0.0076 g, 0.028 mmol) was allowed to react in diethyl ether with 0.5822 g of W-200-B alumina doped with distilled water (10 μL, 0.55 mmol; 20 equiv) for 2 h at ambient temperature. Workup followed by preparative TLC (diethyl ether) afforded 0.0048 g (59%) of *trans*-5,6-dihydroxy-5,6-dihydro-7,12-dimethylbenz-[*a*]anthracene:[19] ^{1}H NMR ($CDCl_3$) δ 1.50–1.80 (b s, 2 H, OH), 2.83 (s, 3 H; 7-Me), 2.93 (s, 3 H; 12-Me), 4.88 (d, J = 3,5 Hz, 1 H; H_5), 5.29 (d, J = 3.5 Hz, 1 H; H_5), 5.29 (d, J = 3.5 Hz, 1 H; H_6), 7.31–8.21 (m, 8 H; Ar H); mass spectrum, *m/e* 290 (parent, molecular ion). Treatment of this diol with acetic anhydride in pyridine at ambient temperature for 24 h followed by conventional workup afforded the trans diacetate derivative, which was recrystallized from ether/hexane (mp 199–200 °C, trans diacetate lit.[19] mp 210–211 °C, *cis* diacetate lit.[19] mp 154–156 °C) and exhibited spectral characteristics in accord with literature[19] values.

DMBA 5,6-Oxide on 2-Methyl-2-propanethiol-Doped Alumina. DMBA 5,6-oxide (0.0126 g, 0.0462 mmol) was allowed to react in diethyl ether with 0.7582 g of W-200-B alumina doped with 2-methyl-2-propanethiol (0.0208 g, 0.231 mmol) for 2 h at ambient temperature. Workup followed by preparative TLC afforded 0.0045 g (33%) of *trans*-5,6-dihydroxy-5,6-dihydro-7,12-dimethylbenz[*a*]anthracene as well as 0.0065 g (39%) of two regioisomeric addition products in a 3:1 ratio by ^{1}H NMR analysis. The predominant isomer was assigned as *trans*-5-hydroxy-6-[(2-methyl-2-propyl)thio]-5,6-dihydro-7,12-dimethylbenz[*a*]-anthracene and the minor isomer was asigned as the *trans*-6-hydroxy-5-[(2-methyl-2-propyl)thio]-5,6-dihydro derivative on the basis of ^{1}H NMR (300 MHz) data in accord with that previously noted.[19]

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Registry No. 1, 89690-57-3; 2, 89690-58-4; 3 (ZR = $PhCH_2NH$), 89690-59-5; 3 (ZR = BuNH), 89690-60-8; 3 (ZR = MeO), 89690-61-9; 3 (ZR = OH), 16644-15-8; 3 (ZR = *t*-BuS), 60731-00-2; 4 (ZR = $PhCH_2NH$), 89690-62-0; 4 (ZR = BuNH), 89690-63-1; 4 (ZR = MeO), 89690-64-2; 4 (ZR = *t*-BuS), 60731-01-3; $PhNH_2$, 62-53-3; $PhCHNH_2$, 100-46-9; $BuNH_2$, 109-73-9; MeOH, 67-56-1; H_2O, 7732-18-5; *t*-BuSH, 75-66-1; DMBA 5,6-oxide, 39834-38-3; alumina, 1344-28-1.

Preparation of Acetylenic Diethyl Acetals from the Ortho Ester $HC(OC_2H_5)_2OC_6H_5$

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The general method of reacting a monosubstituted acetylene with an ortho ester, in the presence of a zinc halide catalyst, has become routinely used for the preparation of acetylenic diethyl acetals in good to excellent yields.[1,2] However, there are some acetals that are either

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